REMARKS

The Office Action has rejected Claims 12-17, 21-22, and 73-77 under 35 U.S.C. § 112, first paragraph, for allegedly being non-enabling. However, it has allowed Claims 23-2, 31, 32 and 78-81.

Applicants have added Claims which, when considered with the comments hereinbelow, are deemed to place the present application in condition for allowance. Favorable consideration is respectfully requested.

At the outset, before addressing the merits, the applicants wish to thank Examiner Gupta for his kindness and courtesy exhibited to their representative and for his helpful suggestions during the telephone interview, which was conducted on October 18, 2005, with applicants' representative.

Before addressing the merits, applicants wish to bring to the attention of the United States Patent and Trademark Office that applicants have amended Claim 12 by deleting superfluous subject matter. In addition applicants have added Claims 82-95. Support for Claims 82-93 is found on page 37, lines 11-26, and original Claims 12 and 23. In addition, Claims 75 and 79 have been amended to make it in conformity with U.S. format; the language preferably t-butyl has been deleted therefrom and placed in new Claims 94 and 95.

No new matter has been added.

Pursuant to the rejection of Claims 12-17, 21-22, and 73-77 under 36 U.S.C. § 112, first paragraph, the Office Action has alleged that the specification, while being enabling for methods for enhancing cognitive functions, does not enable any person skilled in the art to use the invention commensurate in scope with the claims. The Office Actions does not believe that the compounds described in the instant specification provide neuroprotection.

Applicants agree with the United States Patent and Trademark Office that the present application is enabling for methods for enhancing cognitive function. However, contrary to the allegations of the Office Action, the present application is enabling for effecting neuroprotection in a subject.

In order to satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph, a patent application need only teach to one of ordinary skill in the art how to make and use the invention without conducting an undue amount of experimentation. In re Wands 858 F2d 731, 737, 8USPQ2d 1400, 1404 (Fed.Cir. 1988) Experimentation typically engaged in by those of skill in the art is permitted, as long as the experimentation is not undo. Id., In re Angstadt, 537 F2d 498, 504, 190 USPQ 214, 219, (Fed. Cir. 1976).

To determine whether a specification is enabling, various factors are considered. These factors include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of ordinary skill in the art;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples;

(H) The quantity of experimentation needed to make or use the invention or broaden the content of the disclosure.

In re Wands, 858 F2d 731, 737, 8USPQ2d 1400, 1404 (Fed Cir. 1988).

The application of these factors as applied to the present factual situation, as shown hereinbelow, leads to one conclusion – the present application is enabling for providing neuroprotection.

1. The nature of the invention.

The rejected claims are directed, inter alia, to a method of effecting neuroprotection in a subject by administering to a subject in need of treatment an effective amount of a compound recited in Claim 12.

2. The breadth of the claims.

The subject matter in the rejected claims is not over broad, as the application is limited to the use of derivatives of bicyclic 2,5-diketopiperazines for effecting neuroprotection. As will be shown hereinbelow, contrary to the allegations of the United States Patent and Trademark Office, such utility is not unbelievable. There have been many patents which claim a method of effecting neuroprotection. Attached hereto is a list of 51 patents that have issued from the United States Patent and Trademark Office that contains claims for effecting neuroprotection. If the United States Patent and Trademark Office believed such claims were unbelievable, then it would not have granted the listed patents.

3. The relative skill of those in the art.

The relative skill of those in the art is a person who is educated and has experience in the area of neuroprotection.

4. The state of the art.

There are several compounds which have been used for effecting neuroprotection, and these have been patented. These are listed in the attached list. In fact, there are 51 patents which have been issued, some of which is prior art. Some of these, which are representative are discussed below.

For example, U.S. Patent No. 5,661,150 discloses a drug containing a calmodulin inhibitor capable of effecting neuroprotection. It discloses that the compounds are useful for treating or preventing cardiovascular disorders and, cerebral denaturation diseases, including, for example, Alzheimer's disease and Parkinson's disease. Attention is directed to Claim 1 which claims the use of a calmodulin inhibitor for effecting neuroprotection in a subject. (See also, U.S. Patent No. 5,837,706).

U.S. Patent No. 5,859,001 discloses the use of a non-estrogen compound having a terminal phenol group in a four-ring cyclopentanophenanthrene compound having a molecular weight of less than 1000 daltons for effecting neuroprotection. It teaches that the compounds are useful for protecting or treating a neurodegenerative disease, including Parkinson's disease, Alzheimer's disease, Huntington's disease, etc. (See Col. 5, lines 29-46) In fact, attention is directed to Claim 7 thereof which specifically claims the use of these compounds for treating a neurodegenerative disease by conferring neuroprotection in the subject.

Although not specifically prior art, attention is also drawn to more recent patents which have issued. For example, attention is directed to U.S. Patent No. 6,916,835 directed to the use of nitrate esters or a pharmaceutically acceptable salt or ester thereof for effecting neuroprotection. Attention is directed to Claims 1 et seq which recite a method for inhibiting

neurodegeneration or effecting neuroprotection in a subject in need thereof utilizing the nitrate esters described therein.

U.S. Patent No. 6,787,541 discloses, inter alia, thienopyrimidines for use in effecting neuroprotection. Attention is directed to Claim 37 which specifically discloses the use of said compounds for effecting neuroprotection. Attention is also directed to Claim 39,where it lists, various neurodegenerative diseases for which the thieonpyrimidines disclosed therein are effective in treating. These include Parkinson's disease, Alzheimer's disease and Huntington's disease.

As indicated, these are just a few representative patents which have issued that are directed to effecting neuroprotection.

The Office Action however, does not believe that compounds can effect neuroprotection in the case of Alzheimer's disease, for example. In support, it cites an article by Martin which discloses that transient cerebral ischemia produces an irreversible neural death that is not fully understood. Although this reference is interesting, it is irrelevant to the issue of whether the compounds of the present invention are useful for effecting neuroprotection. First, the article does not discuss or even mention any of the bicyclic 2, 5-diketopiperazines disclose in the present application. Consequently, it does not contradict the teachings of the present application regarding the neuroprotection of the 2,5-diketopiperazines disclosed in the present application. Second, case law has constantly held that an inventor is not required to describe or even know why his or her invention works, in order to obtain a patent. Newman v. Quigg, 11 USPQ2d1340, 1345 (Fed Cir. 1989). Thus, an inventor does not need to understand or describe the scientific basis for the practical utility of this invention. Fromson v. Advanced Offset Plates, Inc. 219 USPQ 1137, 140 (Fed. Cir. 1983). Moreover, case law has held that an observation of a

physiological phenomenon is "not inherently suspect simply because the underlying base for the observation cannot be predicted or explained." In re Cartright, 49 UPQ2d 1464 (Fed. Cir. 1992.) Thus, assuming it is true that it is not understood how cerebral ischemia produces irreversible neural cell death, such a conclusion is not inconsistent with the discovery that the 2,5-diketopiperazines described in the present invention are useful for effecting neuroprotection. Even if one does not know how cerebral ischemia produces irreversible neural cell death, one can still find compounds which can effect neuroprotection, as claimed. Moreover, as shown hereinbelow, the record contains both in vitro and in vivo models which show that the compounds of the present invention can effect neuroprotection.

The Office Action also cites Mattson et al. for the statements that there are no treatments that can stop or reverse the inexorable neurodegenerative process in Alzheimer's disease. However, such statements again do not contradict the teachings of the present invention. First, Mattson et al. do not comment on the utility of the bicyclic 2, 5-diketopiperazines described in the present application for effecting neuroprotection. A review of Mattson et al. clearly reveals that there is no mention therein of any bicyclic diketopiperazine. Moreover, the comments referenced above refer to commercial drug on the market; it does not refer to a drug that is being developed. Further, the article refers to commercial utility which is not the same as patentable utility under 35 U.S.C. §§ 101 and 112. Furthermore, as described below, the record has considerable evidence based on in vitro and in vivo tests that compounds of the present invention exhibit neuroprotection from various injury, including, but not limited to ischemic injury, traumatic injury, necrotic injury and apoptotic cell death and the like.

But, most important of all, as indicated above, the applicants have provided references which refute the position of the United States Patent and Trademark Office that there are no

drugs which are effective in neuroprotection. As indicated hereinabove, applicants have provided 51 patents which not only teach that the compounds are useful for effecting neuroprotection but also claim that the compounds therein are effective for effecting neuroprotection in a subject. As described hereinabove, many of them disclose that the compounds therein are useful for treating neurodegenerate diseases including Parkinson's disease and Alzheimer's disease. See, for example, U.S. Patent Nos. 5,837,706; 5,859,001; 6,916,835; and 6,787,541. Thus, contrary to the allegations in the Office Action, there are drugs which are useful in effecting neuroprotection. Therefore, based no the teachings, one of ordinary skill in the art would find it credible that drugs can be used to effect neuroprotection. Moreover, as described hereinbelow, based on the experimental data in the record, one of ordinary skill in the art would conclude that the bicyclic 2,5-diketopiperazines of the present application would be useful for effecting neuroprotection.

5. The level of predictability in the art.

The prior art makes it clear that it is credible that drugs can be useful in effecting neuroprotection, especially if shown by in vitro or in vivo testing in accepted models. As will be described in the next section, the record contains several model systems, using representative drugs of the present invention, which show that bicyclic 2,5-diketopiperazines disclosed in the present application are useful for effecting neuroprotection.

6. The amount of direction provided by the inventor.

The specification provides ample data on test models accepted by one of ordinary skill in the art which shows that the bicyclic 2,5-diketopiparzines disclosed in the present application are useful in effecting neuroprotection in a mammal. For example, attention is directed to the in

vitro and in vivo experiment described in Examples 8 and 9 on Pages 84-97 of the present application which show using representative examples that the bicyclic 2,5-diketopiperazines are useful in effecting neuroprotection.

Example 8 tested the effect of the administration of representative compounds, such as Compound 2a in beam walking and spatial learning of mice after being subjected to traumatic injury from the incision in the brain from a micro-processor-controlled pneumatic impactor. More specifically, the mice were given a representative compound of the present invention, namely compounds of Formula 2a. As shown by the data in Fig. 3, mice treated with Compound 2a began to show chronic neurological recovery as demonstrated by beam walking, within 3 days and were performing this task considerably better 2-3 weeks post injury relative to mice who were not given the drug. In fact, as described on page 88 et seq, mice treated with Compound 2a showed significant improvement in performance of this task than when compared with the controlled mice. Furthermore, as shown by the data and described on Page 89, et seq, mice treated with the representative compound of the present invention were significantly outperforming controlled mice in the beam-walking experiment. See Figure 3 and text accompanying same. In addition, the mice provided with Compound 2a exhibited significantly greater learning relative to the mice in control group (See Fig 6a and 6b). Moreover, as shown in Fig. 7, injured mice treated with Compound 2a had significantly better reference memory function, relative to untreated injured mice, even within 24 hours after trauma (See Fig. 7). Attention is also directed to Example 9 which demonstrates the ability of representative compounds described in the present application for treating neurotrauma in another test animal, rats. Rats subjected to fluid percussion injury and than treated with representative compounds of the present invention showed improved motor recovery. (See Fig 1 and 2).

The allegations in the application regarding the neuroprotection of the diketopiperazines is supported by additional data.

Attention is also directed to the affidavit of Alan Faden, dated October 15, 1999, which provides in vitro evidence using representative compounds of the present invention that the bicyclic 2,5-diketopiperazines block neuronal cell deaths after insults specifically implicated in spinal cord injury and stroke, namely excitotoxic (glutamate induced) and free radical-induced injuries. Further, the data show neuroprotective effects using an in vitro mode of ischemia (stroke) oxygen glucose deprivation (See paragraphs 7-12).

Further, neuroprotective effects were tested using a staurosporine model of apoptotic cell death. As shown by the data in Paragraph 13 therein and the referenced exhibits 4 and 5, the treatment with representative compounds described in the instant application increased survival in the model. Further, attention is directed to Paragraph 14, which is directed to testing the neuroprotection in a traumatic injury model, which is an art accepted model for testing neuroprotective effects of compounds. As shown by the data referenced to in paragraph 14, incubation of cultured cells with a representative compound increased the survival of neuronal cells after traumatic injury. Finally, the neuroprotective effects using a representative compound in the necrotic injury model is described in Paragraph 15 thereof. As described in Paragraph 15 and the referenced data, a representative compound of the present invention improved survival in cultures subject to necrotic insult via maitotoxin.

These results are extremely significant especially since the various pathological mechanisms tested in the experiments described hereinabove have been implicated in causing acute neurodegenerative disorders (i.e., stroke, head injury and spinal cord injury) and have been proposed as potential mechanisms of action for various chronic neurodegenerative disorders

(e.g., Alzheimer's disease, ALS, Huntington's disease). In particular, neuronal apoptosis has been suggested as a mechanism for these chronic neurodegenerative disorders (See, e.g. La Ferla, et al, Nature Genetics, 1995, 9, 21-20; Eladah et al, J. Neuroscience, 1997, 17 (16), 6105-6113, Su et al, NeuroReport 1994, 2529-2533)

Attention is further directed to the Second Declaration of Alan Faden, dated July 9, 2001. This Declaration showed that representative compounds used in the present invention significantly reduce apoptotic cell death caused by beta-amyloid in neuronal cultures. Beta-amyloid, which is a known causative factor in Alzheimer's disease, has been shown to cause significant cell death when added to neuronal culture in vitro (See, eg La Ferla, et al, Nature Genetics 1995, 9, 21-30).

Applicants are also submitting articles which have been reviewed by experts in the field before publication. Attention is directed to the articles by Faden, et al in Journal of Cerebral Blood Flow and Metabolism, 2003, 23, 342-354, which tested the effects of a representative diketopiperazine administered to rats in injury models accepted by the skilled artisan to evaluate the neuroprotective action of drugs. As described in the article, the representative compound significantly reduced cell death associated with necrosis (maitotoxin), apoptosis (Staurosporine) and mechanical injury in neuronal-glial cocultures. It also showed that rats subjected to lateral fluid percussion – induced TBI and then treated with 1 mg/Kg intravenously with the representative compound disclosed in the present application thirty minutes after trauma showed significantly improved motor recovery and spatial learning compared with rats subjected to vehicle treated controls. Treatment with the representative compound also significantly reduced lesion volumes (shown by MRI) and decreased the number of TUNEL-positive neurons observed in ipsilateral hippocampus. Yet, unlike TRH, which is a known neuroprotectant, it did not alter

the mean arterial pressure, body temperature or thyroid stimulating hormone release and did not exhibit analeptic activity. Moreover, unlike TRH, administration of the representative compound did not alter free magnesium concentration or the cellular bioenergetic state. Thus, the article shows that the a representative compound exhibited none of the typical physiologic actions associated with TRH, but possesses neuroprotective actions in vivo and in vitro and attenuates both necrotic and apoptotic cell death.

Faden et al in the Journal of Cerebral Blood Flow and Metabolism, 2003, 23, 355-363, evaluated the effects of treatment with a representative compound in a different animal, mice, subjected to controlled cortical impact brain injury in another model system accepted by one of ordinary skill in the art to the evaluate neuroprotection action of the drug. The treated animals showed significantly enhanced recovery of beam walking and place learning functions compared with controls, in addition to reduced lesion volumes. As demonstrated therein, neuroprotective action was found when the drug was administered initially after thirty minutes, or 1, 4, 8 hours after trauma but not at 24 hours. In another experiment, rats treated with this compound on days 7-10 after injury showed remarkably improved place learning in comparison with injured controls. Thus, the studies showed the neuroprotective effects of the representative compounds in traumatic brain injury.

It is to be noted that these two articles may not present any additional data than that which described in the application or the aforementioned declarations. However, these articles were reviewed by peers and experts in the field. If the data did not show evidence of the neuroprotection of the compound described therein, the peers and experts would have objected to the usage of such description thereof. The fact that they permitted the term neuroprotection

therein shows that one of ordinary skill in the art accepts that these model systems test and show the neuroprotective properties of the compounds tested to therein.

Another article in Neuropharmacology 2005, a copy of which is provided herein is in press but which has been nevertheless will be or has also been published. It also has been peer reviewed. It discloses the neuroprotective activity of three additional representative compounds disclosed in the present application in multiple in vitro models of neuronal injury and after controlled cortical impact in mice. In the studies described therein, the compounds were tested over a range of doses in well characterized in vitro models of necrosis and apoptosis, as well as in a mouse model of controlled cortical impact TBI. Further, the authors examined whether treatment effects might be mediated through changes in the expression patterns for endogenous neurotoxic and/or neuroprotective factors, after injury, using high density oligonucleotide micro arrays. Further, in vitro calcium imaging was used to examine whether the neuroprotective actions of the compounds were associated with reduced changes for the cation.

As shown therein, these three additional compounds showed that they reduced cell death after direct physical trauma or trophic withdrawal. Representative compounds also protected against glutamate toxicity and β-amyloid – induced injury, both of which are well established models to test the ability of a drug to effect neuroprotection. Representative compounds also strongly inhibited glutamate – induced increases in intracellular calcium. As shown, treatment with each of the test compounds resulted in highly significant improvement of motor and cognitive recovery after CCI, and exhibited marked reduced lesion volumes, as shown by high field magnetic resononic imaging. DNA microarray studies following fluid percussion induced traumatic brain injury (TBI) in rats showed that treatment with representative compounds of the present invention after injury significantly down regulated expression of mRNA's for cell cycle

proteins, aquaporins, cathepsins and calpain in ipsilateral cortex and/or hippocampus, while up-regulating expression of brain derived neurotrophic factor, hypoxia-inducible factor and several heat – shock proteins.

As described in the article by Yakovlev et al in the Journal of the American Society Experimental NeuroTherpeutics, 2004, 5-16, these results are important since it has been recognized that cell death phenotypes and their molecular mechanisms are highly diverse. There is caspase dependent apoptosis involved in programmed cell death. Moreover, there are both caspase dependent and caspase independent forms of apoptosis, which may differ morphologically as well as mechanistically. There are also necrotic-like phenotypes that require de novo protein synthesis and are therefore forms of programmed cell death. Moreover, forms of cell death showing certain morphological features of both necrosis and apoptosis have been identified, and termed aponecrosis. Thus, in determining the neuroprotections of a specific drug, it is important to use models that target different cell death cascades.

The data in the article in Neuropharmacology addresses these different types of mechanisms. The trophic withdrawal and β-amyloid toxicity reflects caspase mediated cell death. Trophic withdrawal involves largely caspase-3, whereas β-amyloid toxicity involves multiple caspases and may also reflect translocation of AIF, a caspase independent mitochondrial factor. The punch model utilized in the study of mechanical in vitro trauma is highly predictive of neuroprotection in rodent TBI models. Glutamate induced neurotoxicity is a well established model for testing neuroprotection of drugs. Increased expression of cell cycle genes is associated with caspase mediated neuronal apoptosis in vitro and in vivo.

Thus, the data, when taken together, show that the diketopiperazines described in the present application, have considerable neuroprotective activity.

The Office Action alleges that there is no data that the compounds can effectively provide neoroprotection against amyloid deposition. As described hereinabove, beta-amyloid is a known causative factor in Alzheimer's disease.

Attention is directed to the article in Neuropharmacology discussed hereinabove and to the article by Faden et al., Journal of Alzheimer's Disease, 2004, S93-97 which show that representative compounds disclosed in the present application reduce β-amyloid induced neuronal cell death in culture. Moreover, they exhibit neuroprotection in models of glutamate neurotoxicity as well as other models of necrotic cell death, such as that caused by maitotoxin oxygen glucose deprivation. Since there is strong evidence for the role of glutamate-mediated excitotoxicity in experimental TBI and both amyloid β and head injury have been implicated in the pathology of Alzheimer's disease, these data disclose to one of ordinary skill in the art that the diketopiperazines compounds described in the present application are useful for the treatment of Alzheimer's disease.

Thus, taken together, all of these data evidence the neuroprotection of the diketopiperazines utilized in the present invention.

In evaluating these data, one must not lose sight that any data provided herein which are not specifically disclosed in the specification are used to demonstrate the neuroprotective ability of the diketopiperazines. The specific teachings and the means for demonstrating the neuroprotection of the diketopiperazines are described in the application. The data in the affidavits and the articles described herein support the allegations in the application regarding the neuroprotection of the diketopiperazines disclosed therein. The data was obtained by following the teachings in the specification using techniques and models known to one of ordinary skill in the art.

7. The existence of working examples

The specification provides not only general methods for synthesis of the deketopiperazines (See page 45 line 20 to Page 47, line 20), but also provides examples that describe the preparation of specific compounds with neuroprotective activity (See Page 63, line 1 to Page 67, line 5). The application also provide methods for testing the 2,5-diketopiperazines described therein for testing the compounds for neuroprotective activity (See, Page 53, line 35, to Page 54, line 20).

As described hereinabove, the application contains working examples (Example 8 and 9) evidencing the neuroprotection of the 2,5-diketopiperazines disclosed in the present application using art accepted models. These are supplemented by the data in the Declarations and the data in the aforementioned publications.

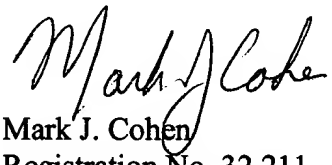
8. The quantity of experimentation needed to make of use the inventions based on the content of the disclosure

Based upon the teachings in the present application and confirmed by the data in the Declarations and the articles, only one conclusion can be drawn -- the amount of experimentation required to make or use the present invention is not undue. Thus, based upon the record, it is clear that the present invention, as taught in the instant application, is enabling for providing neuroprotection in a subject.

Accordingly, for the reasons provided, the rejection of Claims 12-17, 21, 22, and 73-77 under 35 USC § 112, first paragraph is overcome; withdrawal thereof is respectfully requested.

Thus, in view of the Remarks hereinabove, it is respectfully submitted that the present application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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